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L15: Entry 53 of 140 File: USPT Feb 20, 2001

US-PAT-NO: 6190669
DOCUMENT-IDENTIFIER: US 6190669 B1

TITLE: Attenuated mutants of salmonella which constitutively express the Vi antigen

DATE-ISSUED: February 20, 2001

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Noriega; Fernando R.	Baltimore	MD		
Sztein; Marcelo B.	Columbia	MD		
Levine; Myron M.	Columbia	MD		

US-CL-CURRENT: 424/258.1; 424/831, 424/93.1, 424/93.2, 424/93.4, 424/93.48, 435/879

CLAIMS:

What is claimed:

1. An attenuated Salmonella mutant, wherein said mutant constitutively expresses Vi antigen, and wherein in said mutant, the vipR promoter is replaced by a constitutive promoter, so as to cause constitutive expression of viaB.

2. The attenuated Salmonella mutant of claim 1, wherein said mutant is a Salmonella typhi mutant.

3. The attenuated Salmonella mutant of claim 1 or 2, wherein in said mutant, the vipR promoter is replaced by a promoter selected from the group consisting of P.sub.tac, P.sub.trc, P.sub.Olac and P.sub.lpp, so as to cause constitutive expression of viaB.

4. The attenuated Salmonella mutant of claim 1 or 2, wherein said mutant is incapable of forming de novo guanine nucleotides, due to mutation in the guaB-A operon.

5. The attenuated Salmonella mutant of claim 4, wherein said mutation in the guaB-A operon is a deletion mutation, and said deletion mutation is in the guaA gene, the guaB gene, or in both the guaA gene and the guaB gene.

6. The attenuated Salmonella mutant of claim 5, wherein said deletion mutation is in both the guaA gene and the guaB gene.

7. The attenuated Salmonella mutant of claim 6, wherein said mutant has an aro.sup.- phenotype.

8. The attenuated Salmonella mutant of claim 2, wherein said Salmonella typhi mutant is derived from parent strain Salmonella typhi CVD 915 (ATCC No. 202115).

9. The attenuated Salmonella mutant of claim 1, wherein said Salmonella mutant is Salmonella typhi CVD 916 (ATCC No. 202116) or Salmonella typhi CVD 909 (ATCC No. 202117).

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L15: Entry 13 of 140 File: USPT Apr 8, 2003

US-PAT-NO: 6544518
DOCUMENT-IDENTIFIER: US 6544518 B1

TITLE: Vaccines

DATE-ISSUED: April 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Friede; Martin	Farnham			GB
Garcon; Nathalie	Wavre			BE
Gerard; Catherine Marie Ghislaine	Rhode Saint Genese			BE
Hermand; Philippe	Court-Saint-Etienne			BE

US-CL-CURRENT: 424/184.1; 424/208.1, 424/228.1, 424/229.1, 424/231.1, 424/249.1, 424/278.1, 424/283.1, 514/25

CLAIMS:

What is claimed is:

1. An adjuvant composition comprising a QS21 and an immunostimulatory oligonucleotide containing an unmethylated CG dinucleotide.

2. An adjuvant composition according to claim 1 further comprising a carrier.

3. An adjuvant composition as claimed in claim 1, wherein said immunostimulatory oligonucleotide comprises a Purine, Purine, C, G, pyrimidine, pyrimidine sequence.

4. An adjuvant composition as claimed in claim 1, wherein said immunostimulatory oligonucleotide is selected from the group comprising: TCC ATG ACG TTC CTG ACG TT (SEQ ID NO:1); TCT CCC AGC GTG CGC CAT (SEQ ID NO:2); ACC GAT GAC GTC GCC GGT GAC GGC ACC ACG (SEQ ID NO:3); TCG TCG TTT TGT CGT TTT GTC GTT (SEQ ID NO:4); TCC ATG ACG TTC CTG ATG CT (SEQ ID NO:5).

5. An adjuvant composition as claimed in claim 1, wherein the immunostimulatory oligonucleotide contains at least two unmethylated CG repeats being separated at least by 3 nucleotides.

6. An adjuvant composition according to claim 5, wherein the immunostimulatory oligonucleotide contains at least two unmethylated CG repeats being separated by 6 nucleotides.

7. An adjuvant composition as claimed in claim 2, wherein said carrier is a particulate carrier selected from the group comprising metallic salt particles, emulsions, polymers, liposomes, ISCOMs.

8. An immunogenic composition comprising an adjuvant composition as claimed in claims 1 or 2, further comprising an antigen.

9. An immunogenic composition as claimed in claim 8, wherein said antigen is

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L15: Entry 34 of 140 File: USPT Aug 20, 2002

US-PAT-NO: 6436407
DOCUMENT-IDENTIFIER: US 6436407 B1

TITLE: Mutant enterotoxin effective as a non-toxic adjuvant

DATE-ISSUED: August 20, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Clements; John D.	New Orleans	LA		
Dickinson; Bonny L.	Boston	MA		

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
The Administrators of the Tulane Educational Fund	New Orleans	LA			02

APPL-NO: 09/ 368618 [PALM]
DATE FILED: August 4, 1999

PARENT-CASE:
This application is a continuation of application Ser. No. 08/790,691 filed Jan. 29, 1997, currently abandoned, which in turn is a continuation-in-part of application Ser. No. 08/296,848 filed Aug. 26, 1994 currently U.S. Pat. No. 6,019,982.

INT-CL: [07] A61 K 39/21, A61 K 39/02, A61 K 45/00, A61 K 39/00, A61 K 1/00

US-CL-ISSUED: 424/208.1; 424/236.1, 424/234.1, 424/235.1, 424/200.1, 424/184.1, 424/278.1, 424/282.1, 530/350, 530/825
US-CL-CURRENT: 424/208.1; 424/184.1, 424/200.1, 424/234.1, 424/235.1, 424/236.1, 424/278.1, 424/282.1, 530/350, 530/825

FIELD-OF-SEARCH: 424/208.1, 424/236.1, 424/184.1, 424/200.1, 424/234.1, 424/278.1, 424/235.1, 424/257.1, 424/241.1, 424/832, 424/282.1, 530/825, 530/350

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	5182109	January 1993	Tamura et al.	

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FOREIGN-PAT-NO	PUBN-DATE	COUNTRY	US-CL
2217600	January 1989	GB	
WO 92/19265	November 1992	WO	
WO 93/13202	July 1993	WO	
WO 95/17211	June 1995	WO	

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ART-UNIT: 1645

PRIMARY-EXAMINER: Devi; S.

ATTY-AGENT-FIRM: Pennie & Edmonds LLP

ABSTRACT:

Methods and compositions are provided herein for the use of a novel mutant form of E. coli heat-labile enterotoxin which has lost its toxicity but has retained its immunologic activity. This enterotoxin is used in combination with an unrelated antigen to achieve an increased immune response to said antigen when administered as part of a vaccine preparation.

14 Claims, 11 Drawing figures

L15: Entry 34 of 140 File: USPT Aug 20, 2002

DOCUMENT-IDENTIFIER: US 6436407 B1
TITLE: Mutant enterotoxin effective as a non-toxic adjuvant

Brief Summary Text (4):
Microbial pathogens can infect a host by one of several mechanisms. They may enter through a break in the integument induced by trauma, they may be introduced by vector transmission, or they may interact with a mucosal surface. The majority of human pathogens initiate disease by the last mechanism, i.e., following interaction with mucosal surfaces. Bacterial and viral pathogens that act through this mechanism first make contact with the mucosal surface where they may attach and then colonize, or be taken up by specialized absorptive cells (M cells) in the epithelium that overlay Peyer's patches and other lymphoid follicles [Bockman and Cooper, 1973, Am. J. Anat. 136:455-477; Owen et al., 1986, J. Infect. Dis. 153:1108-1118]. Organisms that enter the lymphoid tissues may be readily killed within the lymphoid follicles, thereby provoking a potentially protective immunological response as antigens are delivered to immune cells within the follicles (e.g., Vibrio cholerae). Alternatively, pathogenic organisms capable of surviving local defense mechanisms may spread from the follicles and subsequently cause local or systemic disease (i.e., Salmonella spp., poliovirus, rotavirus in immunocompromised hosts).

Brief Summary Text (5):
Secretory IgA (sIgA) antibodies directed against specific virulence determinants of infecting organisms play an important role in overall mucosal immunity [Cebra et al., 1986, In: Vaccines 86, Brown et al. (ed.), Cold Spring Harbor Laboratory, New York. p.p. 129-133]. In many cases, it is possible to prevent the initial infection of mucosal surfaces by stimulating production of mucosal sIgA levels directed against relevant virulence determinants of an infecting organism. Secretory IgA may prevent the initial interaction of the pathogen with the mucosal surface by blocking attachment and/or colonization, neutralizing surface acting toxins, or preventing invasion of the host cells. While extensive research has been conducted to determine the role of cell mediated immunity and serum antibody in protection against infectious agents, less is known about the regulation, induction, and secretion of sIgA. Parenterally administered inactivated whole-cell and whole-virus preparations are effective at eliciting protective serum IgG and delayed type hypersensitivity reactions against organisms that have a significant serum phase in their pathogenesis (i.e., Salmonella typhi, Hepatitis B). However, parenteral vaccines are not effective at eliciting mucosal sIgA responses and are ineffective against bacteria that interact with mucosal surfaces and do not invade (e.g., Vibrio cholerae). There is, however, recent evidence that parenterally administered vaccines may be effective against at least one virus, rotavirus, that interacts primarily with mucosal surfaces [Conner et al., 1993, J. Virol. 67:6633-6641]. Protection is presumed to result from transudation of antigen specific IgG onto mucosal surfaces for virus neutralization. Therefore, mechanisms that stimulate both serum and mucosal antibodies and cell mediated immunity are important for effective vaccines.

Brief Summary Text (7):
A number of strategies have been developed for mucosal immunization, including the use of attenuated mutants of bacteria (i.e., Salmonella spp.) as carriers of heterologous antigens [Cardenas and Clements, 1992, Clin. Microbiol. Rev. 5:328-342; Clements et al., 1992, In: Recombinant DNA Vaccines: Rationale and Strategy, Isaacson (ed.), Marcel Decker, New York. p.p. 293-321; Clements and Cardenas, 1990, Res. Microbiol. 141:981-993; Clements and El-Morshidy, 1984, Infect. Immun. 46:564-569], encapsulation

of antigens into microspheres composed of poly-DL-lactide-glycolide (PGL), protein-like polymers--proteinoids [Santiago et al., 1993, Pharmaceutical Research 10:1243-1247], gelatin capsules, different formulations of liposomes [Alving et al., 1986, Vaccine 4:166-172; Garcon and Six, 1993, J. Immunol. 146:3697-3702; Gould-Fogerite and Mannino, 1993, In: Liposome Technology 2nd Edition. Vol. III, Gregoriadis (ed.)], adsorption onto nanoparticles, use of lipophilic immune stimulating complexes (ISCOMS) [Mowat and Donachie, 1991, Immunology Today 12:383-385], and addition of bacterial products with known adjuvant properties [Clements et al., 1988, Vaccine 6:269-277; Elson, 1989, Immunology Today 146:29-33; Lycke and Holmgren, 1986, Immunology 59:301-308; Lycke et al., 1992, Eur. J. Immunol. 22:2277-2281]. The two bacterial products with the greatest potential to function as mucosal adjuvants are cholera toxin (CT), produced by various strains of V. cholerae, and the heat-labile enterotoxin (LT) produced by some enterotoxigenic strains of Escherichia coli. Although LT and CT have many features in common, these are clearly distinct molecules with biochemical and immunologic differences which make them unique.

Detailed Description Text (17):
The methods and compositions of the present invention are intended for use both in immature and mature vertebrates, in particular birds, mammals, and humans. Useful antigens, as examples and not by way of limitation, would include antigens from pathogenic strains of bacteria (Streptococcus pyogenes, Streptococcus pneumoniae, Neisseria gonorrhoea, Neisseria meningitidis, Corynebacterium diphtheriae, Clostridium botulinum, Clostridium perfringens, Clostridium tetani, Haemophilus influenzae, Klebsiella pneumoniae, Klebsiella ozaenae, Klebsiella rhinoscleromotis, Staphylococcus aureus, Vibrio cholerae, Escherichia coli, Pseudomonas aeruginosa, Campylobacter (Vibrio) fetus, Campylobacter jejuni, Aeromonas hydrophila, Bacillus cereus, Edwardsiella tarda, Yersinia enterocolitica, Yersinia pestis, Yersinia pseudotuberculosis, Shigella dysenteriae, Shigella flexneri, Shigella sonnei, Salmonella typhimurium, Treponema pallidum, Treponema pertenue, Treponema carateneum, Borrelia vincentii, Borrelia burgdorferi, Leptospira icterohemorrhagiae, Mycobacterium tuberculosis, Toxoplasma gondii, Pneumocystis carinii, Francisella tularensis, Brucella abortus, Brucella suis, Brucella melitensis, Mycoplasma spp., Rickettsia prowazeki, Rickettsia tsutsugumushi, Chlamydia spp., Helicobacter pylori; pathogenic fungi (Coccidioides immitis, Aspergillus fumigatus, Candida albicans, Blastomyces dermatitidis, Cryptococcus neoformans, Histoplasma capsulatum); protozoa (Entomoeba histolytica, Trichomonas tenas, Trichomonas hominis, Trichomonas vaginalis, Trypanosoma gambiense, Trypanosoma rhodesiense, Trypanosoma cruzi, Leishmania donovani, Leishmania tropica, Leishmania braziliensis, Pneumocystis pneumonia, Plasmodium vivax, Plasmodium falciparum, Plasmodium malaria); or Helminths (Enterobius vermicularis, Trichuris trichiura, Ascaris lumbricoides, Trichinella spiralis, Strongyloides stercoralis, Schistosoma japonicum, Schistosoma mansoni, Schistosoma haematobium, and hookworms) either presented to the immune system in whole cell form or in part isolated from media cultures designed to grow said organisms which are well known in the art or relevant antigens from said organisms obtained by genetic engineering techniques or by chemical synthesis.

Detailed Description Text (18):
Other relevant antigens would be pathogenic viruses (as examples and not by limitation: Poxviridae, Herpesviridae, Herpes Simplex virus 1, Herpes Simplex virus 2, Adenoviridae, Papovaviridae, Enteroviridae, Picornaviridae, Parvoviridae, Reoviridae, Retroviridae, influenza viruses, parainfluenza viruses, mumps, measles, respiratory syncytial virus, rubella, Arboviridae, Rhabdoviridae, Arenaviridae, Hepatitis A virus, Hepatitis B virus, Hepatitis C virus, Hepatitis E virus, Non-A/Non-B Hepatitis virus, Rhinoviridae, Coronaviridae, Rotoviridae, and Human Immunodeficiency Virus) either presented to the immune system in whole or in part isolated from media cultures designed to grow such viruses which are well known in the art or relevant antigens therefrom obtained by genetic engineering techniques or by chemical synthesis.

Detailed Description Text (19):
Further examples of relevant antigens include, but are not limited to, vaccines. Examples of such vaccines include, but are not limited to, influenza vaccine, pertussis vaccine, diphtheria and tetanus toxoid combined with pertussis vaccine, hepatitis A vaccine, hepatitis B vaccine, hepatitis C vaccine, hepatitis E vaccine, Japanese encephalitis vaccine, herpes vaccine, measles vaccine, rubella vaccine, mumps

vaccine, mixed vaccine of measles, mumps and rubella, papillomavirus vaccine, parvovirus vaccine, respiratory syncytial virus vaccine, Lyme disease vaccine, polio vaccine, malaria vaccine, varicella vaccine, gonorrhea vaccine, HIV vaccine, schistosomiasis vaccine, rotavirus vaccine, mycoplasma vaccine, pneumococcal vaccine, meningococcal vaccine and others. These can be produced by known common processes. In general, such vaccines comprise either the entire organism or virus grown and isolated by techniques well known to the skilled artisan or comprise relevant antigens of these organisms or viruses which are produced by genetic engineering techniques or chemical synthesis. Their production is illustrated by, but not limited to, as follows:

Detailed Description Text (24):
Hepatitis B vaccine: a vaccine comprising the whole or part of an antigen protein which is obtained by isolating and purifying the HBs antigen by salting-out or ultracentrifugation, obtained from hepatitis carrying blood, or by genetic engineering techniques or by chemical synthesis.

Detailed Description Text (49):
Use of purified antigens as vaccine preparations can be carried out by standard methods. For example, the purified antigens should be adjusted to an appropriate concentration, formulated with an adjuvant-effective amount of mLT and packaged for use. The immunogen may also be incorporated into liposomes, or conjugated to polysaccharides and/or other polymers for use in a vaccine formulation.

Other Reference Publication (16):
Cardenas and Clements, 1992, "Oral immunization using live attenuated Salmonella spp. as carriers of foreign antigens", Clin. Microbiol. Rev. 5(3):328-342.

Other Reference Publication (25):
Clements and Cardenas, 1990, "Vaccines against enterotoxigenic bacterial pathogens based on hybrid Salmonella that express heterologous antigens", Res. Microbiol. 141:981-993.

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L15: Entry 41 of 140 File: USPT Apr 16, 2002

US-PAT-NO: 6372227
DOCUMENT-IDENTIFIER: US 6372227 B1

TITLE: Vaccines

DATE-ISSUED: April 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE ZIP CODE	COUNTRY
Garcon; Nathalie	Wavre		BE
Momin; Patricia Marie Christine Aline Francoise	Brussells		BE

US-CL-CURRENT: 424/283.1; 424/184.1, 424/278.1, 514/937, 514/938, 514/943

CLAIMS:

What is claimed is:

1. A composition comprising an oil in water emulsion having an oil phase and an aqueous phase and a saponin, wherein the oil phase of said oil in water emulsion comprises a metabolizable oil and a sterol and the saponin is in the aqueous phase.

2. A composition as claimed in claim 1, where the sterol is cholesterol.

3. A composition as claimed in claim 1, wherein said metabolizable oil is squalene.

4. A composition as claimed in claim 1, wherein said saponin is a derivate of QuliA.

5. A composition as claimed in claim 4, wherein said QuilA derivative is selected from the group consisting of QS21 and QS17.

6. A composition as claimed in claim 1, further containing one or more other immunomodulators.

7. A composition as claimed in claim 6, wherein the immunomodulators are selected from the group consisting of 3D-MPL and .alpha.-tocopherol.

8. A composition for raising an immune response comprising a composition as claimed in any one of claims 1 to 7, further comprising an antigen or antigenic preparation.

9. A composition for raising an immune response as claimed in claim 8, where the antigen or antigenic preparation is prepared from the group comprising: Human Immunodeficiency Virus; Herpes Simplex Virus type 1; Herpes Simplex Virus type 2, Human Cytomegalovirus; Hepatitis A, B, C or E; Respiratory Syncytial Virus, Human Papilloma Virus; Influenza Virus, Salmonella, Neisseria,; Borrelia; Chlamydia; Bordetella; Plasmodium, Toxoplasma, tuberculosis and EBV.

10. A composition for raising an immune response as claimed in claim 8, wherein the antigen or antigenic preparation is a combination of the Malaria antigens

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L15: Entry 41 of 140 File: USPT Apr 16, 2002

US-PAT-NO: 6372227
DOCUMENT-IDENTIFIER: US 6372227 B1

TITLE: Vaccines

DATE-ISSUED: April 16, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Garcon; Nathalie	Wavre			BE
Momin; Patricia Marie Christine Aline Francoise	Brussells			BE

ASSIGNEE-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY	TYPE CODE
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APPL-NO: 09/ 486996 [PALM]
DATE FILED: April 24, 2000

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	9718901	September 5, 1997

PCT-DATA:

APPL-NO	DATE-FILED	PUB-NO	PUB-DATE	371-DATE	102(E)-DATE
PCT/EP98/05714	September 2, 1998	WO99/12565	Mar 18, 1999	Apr 24, 2000	Apr 24, 2000

INT-CL: [07] A61 K 45/00, A61 K 47/44

US-CL-ISSUED: 424/283.1; 424/184.1, 424/278.1, 424/283.1, 514/937, 514/938, 514/943
US-CL-CURRENT: 424/283.1; 424/184.1, 424/278.1, 514/937, 514/938, 514/943

FIELD-OF-SEARCH: 424/455, 424/184.1, 424/278.1, 424/283.1, 514/937, 514/938, 514/943

PRIOR-ART-DISCLOSED:

U.S. PATENT DOCUMENTS

Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
☐	4806350	February 1989	Gerber	424/88
☐	5585103	December 1996	Raychaudhuri et al.	424/278.1
☐	6270769	August 2001	Raychaudhuri et al.	424/184.1

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L15: Entry 41 of 140 File: USPT Apr 16, 2002

DOCUMENT-IDENTIFIER: US 6372227 B1
TITLE: Vaccines

Drawing Description Text (9):
FIG. 8 shows the titres of anti-Hepatitis B virus antibody responses (Ig) expressed as both individual mouse sera and average (21 days post II).

Detailed Description Text (9):
Preferably the vaccine formulations of the present invention contain an antigen or antigenic composition capable of eliciting an immune response against a human pathogen, which antigen or antigenic composition is derived from HIV-1, (such as tat, nef, gp120 or gp160), human herpes viruses, such as gD or derivatives thereof or Immediate Early protein such as ICP27 from HSV1 or HSV2, cytomegalovirus ((esp Human)(such as gB or derivatives thereof), Rotavirus (including live-attenuated viruses), Epstein Barr virus (such as gp350 or derivatives thereof), Varicella Zoster Virus (such as gpI, II and IE63), or from a hepatitis virus such as hepatitis B virus (for example Hepatitis B Surface antigen or a derivative thereof), hepatitis A virus, hepatitis C virus and hepatitis E virus, or from other viral pathogens, such as paramyxoviruses: Respiratory Syncytial virus (such as F and G proteins or derivatives thereof), parainfluenza virus, measles virus, mumps virus, human papilloma viruses (for example HPV6, 11, 16, 18, . . .), flaviviruses (e.g. Yellow Fever Virus, Dengue Virus, Tick-borne encephalitis virus, Japanese Encephalitis Virus) or Influenza virus, or derived from bacterial pathogens such as Neisseria spp, including N. gonorrhea and N. meningitidis (for example capsular polysaccharides and conjugates thereof, transferrin-binding proteins, lactoferrin binding proteins, PilC, adhesins); Streptococcus spp, including S. pneumoniae (for example capsular polysaccharides and conjugates thereof, PsaA, PspA, streptolysin, choline-binding proteins), S. pyogenes (for example M proteins or fragments thereof, C5A protease, lipoteichoic acids), S. agalactiae, S. mutans; Haemophilus spp, including H. influenzae type B (for example PRP and conjugates thereof), non typeable H. influenzae (for example OMP26, high molecular weight adhesins, P5, P6, lipoprotein D), H. ducreyi; Moraxella spp, including M catarrhalis, also known as Branhamella catarrhalis (for example high and low molecular weight adhesins and invasins); Bordetella spp, including B. pertussis (for example pertactin, pertussis toxin or derivatives thereof, filamenteous hemagglutinin, adenylate cyclase, fimbriae), B. parapertussis and B. bronchiseptica; Mycobacterium spp., including M. tuberculosis (for example ESAT6, Antigen 85A, -B or -C), M. bovis, M. leprae, M. avium, M. paratuberculosis, M. smegmatis; Legionella spp, including L. pneumophila; Escherichia spp, including enterotoxic E. coli (for example colonization factors, heat-labile toxin or derivatives thereof, heat-stable toxin or derivatives thereof), enterohemorragic E. coli, enteropathogenic E. coli (for example shiga toxin-like toxin or derivatives thereof); Vibrio spp, including V. cholera (for example cholera toxin or derivatives thereof), Shigella spp, including S. sonnei, S. dysenteriae, S. flexnerii; Yersinia spp, including Y. enterocolitica (for example a Yop protein), Y. pestis, Y. pseudotuberculosis, Campylobacter spp, including C. jejuni (for example toxins, adhesins and invasins) and C. coli; Salmonella spp, including S. typhi, S. paratyphi, S. choleraesuis, S. enteritidis; Listeria spp., including L. monocytogenes; Helicobacter spp, including H. pylori (for example urease, catalase, vacuolating toxin); Pseudomonas spp, including P. aeruginosa, Staphylococcus spp., including S. aureus, S. epidermidis; Enterococcus spp., including E. faecalis, E. faecium; Clostridium spp., including C. tetani (for example tetanus toxin and derivative thereof), C. botulinum (for example botulinum toxin and derivative thereof, C. difficile (for example clostridium toxins A or B and derivatives thereof); Bacillus

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L15: Entry 53 of 140 File: USPT Feb 20, 2001

US-PAT-NO: 6190669
DOCUMENT-IDENTIFIER: US 6190669 B1

TITLE: Attenuated mutants of salmonella which constitutively express the Vi antigen

DATE-ISSUED: February 20, 2001

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APPL-NO: 09/ 076761 [PALM]
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INT-CL: [07] A61 K 39/112

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US-CL-CURRENT: 424/258.1; 424/831, 424/93.1, 424/93.2, 424/93.4, 424/93.48, 435/879

FIELD-OF-SEARCH: 424/184.1, 424/234.1, 424/258.1, 424/93.1, 424/93.4, 424/831, 424/93.48, 424/93.2, 935/33, 935/41, 935/38, 435/822, 435/879

PRIOR-ART-DISCLOSED:

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Search Selected | Search ALL

	PAT-NO	ISSUE-DATE	PATENTEE-NAME	US-CL
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☐	5783196	July 1998	Noriega	424/234.1

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ART-UNIT: 163

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ABSTRACT:

Attenuated Salmonella mutants which constitutively express the Vi antigen are disclosed, as well as vaccines against typhoid fever containing the same, live vector vaccines containing the same, and DNA-mediated vaccines containing the same.

23 Claims, 17 Drawing figures

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L15: Entry 53 of 140 File: USPT Feb 20, 2001

DOCUMENT-IDENTIFIER: US 6190669 B1
TITLE: Attenuated mutants of salmonella which constitutively express the Vi antigen

Abstract Text (1):
Attenuated Salmonella mutants which constitutively express the Vi antigen are disclosed, as well as vaccines against typhoid fever containing the same, live vector vaccines containing the same, and DNA-mediated vaccines containing the same.

Brief Summary Text (2):
The present invention relates to attenuated Salmonella mutants which constitutively express the Vi antigen, as well as vaccines against typhoid fever containing the same, live vector vaccines containing the same, and DNA-mediated vaccines containing the same.

Brief Summary Text (5):
The Vi antigen, a capsular polysaccharide, was first described by Felix et al, Lancet, 227:186-191 (1934). This capsular polysaccharide is present in Salmonella, such as S. typhi, S. paratyphi C, and S. dublin, as well as in Citrobacter freundii. Structurally, the Vi antigen is a linear polymer of .beta.-4,2-deoxy-2N-acetylgalacturonic acid with variable O-acetylation (Daniels et al, Infect. Immun., 57:3159-3164 (1989)). Its presence in S. typhi has been correlated, in vitro, with a significant decrease in lysis by serum, complement activation and phagocytosis (Looney et al, J. Lab. Clin. Med., 108:506-516 (1986)). Thus, the Vi antigen may act as a shield protecting S. typhi against the immune system.

Brief Summary Text (7):
Three widely separated chromosomal loci, viaA, viaB, and ompB are thought to be necessary for expression of the Vi antigen (Johnson et al, J. Bacteriol., 90:302-308 (1965); and Snellings et al, J. Bacteriol., 145:1010-1017 (1981)). Of these, the viaB locus is always found in Vi antigen-positive strains, and is thought to contain the genes encoding the enzymes necessary for the synthesis of Vi (Hashimoto et al, J. Bacteriol., 175:4456-4465 (1993); and Virlogeux et al, Microbiol., 141:3039-3047 (1995)). The viaB locus consists of 11 open reading frames (ORF) (FIG. 1A), of which the vipA and vipB genes encode the enzymes that synthesize the nucleotide sugar of the Vi polysaccharide, and the five vex genes (vexA-E) are thought to be responsible for translocation of the Vi antigen (Hashimoto et al (1993), supra). The first ORF of the viaB region, i.e., vipR (FIG. 1A), is a positive transcriptional regulator for its own expression, as well as for the expression of vipA, vipB, orf4, vipC, and perhaps others genes downstream of vipR (Hashimoto et al, J. Bacteriol., 178:1430-1436 (1996)). Furthermore, the promoter upstream of vipR also controls the transcription of (at least) vipA and vipB (encoding structural units of the Vi antigen), forming an operon within the viaB region. Another chromosomal region, the ompB operon, comprising the ompR-envZ genes, plays a role in the expression of the Vi antigen as a transcriptional regulator of viaB (Pickard et al, Infect. Immun., 62:3984-3993 (1994)). The ompR-envZ region forms part of the adaptive response of E. coli to conditions of high osmolarity. In S. typhi, the Vi antigen is osmotically regulated and ompR is necessary for its expression (Pickard et al, supra).

Brief Summary Text (9):
The Vi capsular polysaccharide of S. typhi is a virulence factor and a protective antigen in humans (Felix et al (1934), supra). Purified Vi polysaccharide is a

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L19: Entry 6 of 43 File: USPT Sep 18, 2001

US-PAT-NO: RE37381
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TITLE: Vaccine against hepatitis A virus

DATE-ISSUED: September 18, 2001

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US-CL-CURRENT: 424/226.1; 435/235.1, 435/237, 536/23.72

CLAIMS:

What is claimed is:

1. An attenuated hepatitis A virus .[.comprising a.]. .Iadd.whose .Iaddend.genome .Iadd.has a cDNA sequence according to FIG. 1 .Iaddend..[.characterized by the following nucleotides: cytosine at.]. .Iadd.except for nucleotide .Iaddend.positions 3919, 4043, 4222 and 4810; .Iadd.which have cytosines as bases; .Iaddend..[.guanine at.]. .Iadd.nucleotide .Iaddend.positions 964 and 3196 .Iadd.which have guanines as bases.Iaddend.; .[.adenine at.]. .Iadd.nucleotide .Iaddend.positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 .Iadd.which have adenines as bases.Iaddend.; and .[.thymine at.]. .Iadd.nucleotide .Iaddend.positions 3025, 3889, 4087 and 5232 .Iadd.which have thymines as bases.Iaddend..

2. The attenuated hepatitis A virus of claim 1 wherein .[.said genome encodes the following amino acids: an arginine is encoded at nucleotide.]. .Iadd.the base change at .Iaddend.position 964 .Iadd.results in a codon which encodes arginine.Iaddend.; .[.valine at nucleotide.]. .Iadd.the base changes at .Iaddend.positions .Iadd.3025 and 3889 result in codons which encode valine; the base changes at positions .Iaddend.3196, 4222 and 4810 .Iadd.result in codons which encode serine.Iaddend.; .[.alanine at.]. .Iadd.the base change at .Iaddend.position 3919 .Iadd.results in a codon which encodes an alanine.Iaddend.; .[.methionine at.]. .Iadd.the base change at .Iaddend.position 4087 .Iadd.results in a codon which encodes a methionine.Iaddend.; .[.lysine at.]. .Iadd.the base change at .Iaddend.position 4185 .Iadd.results in a codon which encodes a lysine.Iaddend.; .[.isoleucine at.]. .Iadd.the base change at .Iaddend.position 4563 .Iadd.results in a codon which encodes an isoleucine.Iaddend.; .[.tyrosine at.]. .Iadd.the base change at .Iaddend.position 5232 .Iadd.results in a codon which encodes a tyrosine.Iaddend.; .[.asparagine at.]. .Iadd.the nucleotide change at .Iaddend.position 6147 .Iadd.results in a codon which encodes an asparagine.Iaddend.; and .[.threonine at.]. .Iadd.the

nucleotide change at .Iaddend.position 6522 .Iadd.results in a codon which encodes a threonine.Iaddend..

3. A tissue culture adapted hepatitis A virus .[.comprising a.]. .Iadd.whose .Iaddend.genome .Iadd.has a cDNA sequence according to FIG. 1 .Iaddend..[.characterized by a cytosine at.]. .Iadd.except for .Iaddend.nucleotide position 3191 .Iadd.which has cytosine as a base .Iaddend.and .[.a thymine at.]. nucleotide position 3889 .Iadd.which has thymine as a base.Iaddend..

4. The tissue culture adapted hepatitis A virus of claim 3 wherein .[.said genome encodes the following amino acids: an alanine at nucleotide.]. .Iadd.the base change at .Iaddend.position 3919 .Iadd.results in a codon which encodes an alanine .Iaddend.and .[.a valine at nucleotide.]. .Iadd.the base change at .Iaddend.position 3889 .Iadd.results in a codon which encodes a valine.Iaddend..

5. A pharmaceutical composition, comprising .Iadd.an .Iaddend.immunogenic amount of the virus of claim 4 and pharmaceutically acceptable carrier.

6. A method for inducing protective immunity against HAV, comprising administering to a host susceptible to HAV infection, immunogenic amount of hepatitis A virus comprising a genome coding for alanine at nucleotide position 3919 and valine at nucleotide position 3889, to render said host immune to HAV infection..Iadd.

7. An isolated nucleic acid molecule comprising sequence according to FIG. 1 where said sequence encodes HAV HM-175 wild-type hepatitis A virus..Iaddend..Iadd.

8. A nucleic acid molecule encoding an attenuated hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide positions 3919, 4043, 4222 and 4810 which have cytosines as bases; nucleotide positions 964 and 3196 which have guanines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; and nucleotide positions 3025, 3889, 4087 and 5232 which have thymines as bases..Iaddend..Iadd.

9. A nucleic acid molecule encoding an attenuated hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide positions 3919, 4043 and 4222 which have cytosines as bases, nucleotide positions 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; and nucleotide positions 3889, 4087 and 5232 which have thymines as bases..Iaddend..Iadd.

10. A nucleic acid molecule encoding an attenuated hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide positions 3919, 4043 and 4222 which have cytosines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3025, 3889, 4087 and 5232 which have thymines as bases, and nucleotide positions 964 and 3196 which have guanines as bases..Iaddend..Iadd.

11. An attenuated hepatitis A virus whose genome has a cDNA sequence according to FIG. 1 except for nucleotide positions 3919, 4043 and 4222 which have cytosines as bases, nucleotide positions 4185, 4563, 5204, 6147 and 6522 which have adenines as bases, and nucleotide positions 3889, 4087 and 5232 which have thymines as bases..Iaddend..Iadd.

12. A vaccine comprising an immunologically effective amount of the virus according to claim 11 in a pharmaceutically acceptable carrier or diluent..Iaddend..Iadd.

13. An attenuated hepatitis A virus whose genome as a cDNA sequence according to FIG. 1 except for nucleotide positions 3919, 4043 and 4222 which have cytosines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3025, 3889, 4087 and 5232 which have thymines as bases; and nucleotide positions 964 and 3196 which have guanines as

bases..Iaddend..Iadd.

14. A vaccine comprising an immunologically effective amount of the virus according to claim 13 in a pharmaceutically acceptable carrier or diluent..Iaddend..Iadd.

15. A nucleic acid molecule encoding a tissue culture adapted hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide position 3919 which has cytosine as a base and nucleotide position 3889 which has thymine as a base..Iaddend..Iadd.

16. A nucleic acid molecule encoding an attenuated hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide positions 131-134 which are deleted, and nucleotide positions 203-207 from which a single thymine is deleted; nucleotide positions 124, 3919, 4043 and 4222 which have cytosines as bases, nucleotide positions 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3889, 4087 and 5232 which have thymines as bases; and nucleotide position 152 which has a guanine as a base..Iaddend..Iadd.

17. An attenuated hepatitis A virus whose genome has a cDNA sequence according to FIG. 1 except for nucleotide positions 131-134 which are deleted, nucleotide positions 203-207 from which a single thymine is deleted; nucleotide positions 124, 3919, 4043 and 4222 which have cytosines as bases, nucleotide positions 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3889, 4087 and 5232 which have thymines as bases; and nucleotide position 142 which has a guanine as a base..Iaddend..Iadd.

18. A vaccine comprising an immunologically effective amount of a virus according to claim 17 in a pharmaceutically acceptable carrier or diluent..Iaddend..Iadd.

19. A nucleic acid molecule encoding an attenuated hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide positions 131-134 which are deleted, at nucleotide positions 203-207 from which a single thymine is deleted; nucleotide positions 124, 3919, 4043 and 4222 which have cytosines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; and nucleotide positions 3889, 4087 and 5232 which have thymines as bases, nucleotide positions 152, 964 and 3196 which have guanines as bases..Iaddend..Iadd.

20. An attenuated hepatitis A virus whose genome has a cDNA sequence according to FIG. 1 except for nucleotide positions 131-134 which are deleted, nucleotide positions 203-207 from which a single thymine is deleted; nucleotide positions 124, 3919, 4043 and 4222 which have cytosines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3889, 4087 and 5232 which have thymines as bases; nucleotide positions 152, 964 and 3196 which have guanine as bases..Iaddend..Iadd.

21. A vaccine comprising an immunologically effective amount of a virus according to claim 20 in a pharmaceutically acceptable carrier or diluent..Iaddend..Iadd.

22. An attenuated hepatitis A virus whose genome has a cDNA sequence according to FIG. 1 except for nucleotide positions 3919, 4043 and 4222 which have cytosines as bases; nucleotide positions 964 and 3196 which have guanines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3025, 3889, 4087 and 5232 which have thymines as bases..Iaddend..Iadd.

23. The attenuated hepatitis A virus of claim 22 wherein the base change at position 964 results in a codon which encodes arginine; the base changes at positions 3025 and 3889 result in codons which encode valine; the base changes at positions 3196 and 4222 result in codons which encode serine; the base change at position 3919 results in a codon which encodes an alanine; the base change at position 4087 results in a codon which encodes a methionine; the base change at position 4185 results in a codon which encodes a lysine; the base change at

position 4563 results in a codon which encodes an isoleucine; the base change at position 5232 results in a codon which encodes a tyrosine; the base change at position 6147 results in a codon which encodes an asparagine; and the base change at position 6522 results in a codon which encodes a threonine..Iaddend..Iadd.

24. A nucleic acid molecule encoding an attenuated hepatitis A virus, said molecule having a nucleotide sequence according to FIG. 1 except for nucleotide positions 3919, 4043 and 4222 which have cytosines as bases; nucleotide positions 964 and 3196 which have guanines as bases; nucleotide positions 1742, 2864, 4185, 4563, 5204, 6147 and 6522 which have adenines as bases; nucleotide positions 3025, 3889, 4087 and 5232 which have thymines as bases..Iaddend.